



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : C12N 15/12, C07K 14/47, C12Q 1/68, C07K 16/18		A3	(11) International Publication Number: <b>WO 99/58675</b> (43) International Publication Date: 18 November 1999 (18.11.99)															
(21) International Application Number: PCT/US99/10602 (22) International Filing Date: 13 May 1999 (13.05.99)  (30) Priority Data: <table border="0"> <tr> <td>60/085,426</td> <td>14 May 1998 (14.05.98)</td> <td>US</td> </tr> <tr> <td>60/085,537</td> <td>15 May 1998 (15.05.98)</td> <td>US</td> </tr> <tr> <td>60/085,696</td> <td>15 May 1998 (15.05.98)</td> <td>US</td> </tr> <tr> <td>60/105,234</td> <td>21 October 1998 (21.10.98)</td> <td>US</td> </tr> <tr> <td>60/105,877</td> <td>27 October 1998 (27.10.98)</td> <td>US</td> </tr> </table> (71) Applicants: CHIRON CORPORATION [US/US]; 4560 Horton Street - R440, Emeryville, CA 94608 (US). HYSEQ INC. [US/US]; 675 Almanor Avenue, Sunnyvale, CA 94086 (US). (72) Inventors: WILLIAMS, Lewis, T.; 3 Miroflores, Tiburon, CA 94920 (US). ESCOBEDO, Jaime; 1470 Lavorna Road, Alamo, CA 94507 (US). INNIS, Michael, A.; 315 Constance Place, Moraga, CA 94556 (US). GARCIA, Pablo, Dominguez; 882 Chenery Street, San Francisco, CA 94131 (US). SUDDUTH-KLINGER, Julie; 280 Lexington Road, Kensington, CA 94707 (US). REINHARD, Christoph; 1633 Clinton Avenue, Alameda, CA 94501 (US). GIESE, Klaus; Chausseestrasse 92, D-10115 Berlin (DE). RANDAZZO, Filippo; Apartment 403, 690 Chestnut Street, San Francisco, CA 94133 (US). KENNEDY, Giulia, C.; 360 Castenada Av- 		60/085,426	14 May 1998 (14.05.98)	US	60/085,537	15 May 1998 (15.05.98)	US	60/085,696	15 May 1998 (15.05.98)	US	60/105,234	21 October 1998 (21.10.98)	US	60/105,877	27 October 1998 (27.10.98)	US	<p>enue, San Francisco, CA 94116 (US). POT, David; 1565 5th Avenue #102, San Francisco, CA 94112 (US). KASSAM, Altaf; 2659 Harold Street, Oakland, CA 94602 (US). LAMSON, George; 232 Sandringham Drive, Moraga, CA 94556 (US). DRMANAC, Radoje; 850 East Greenwich Place, Palo Alto, CA 94303 (US). CRKVENJAKOV, Radomir; 762 Haverhill Drive, Sunnyvale, CA 94068 (US). DICKSON, Mark; 1411 Gabilan Drive #B, Hollister, CA 95025 (US). DRMANAC, Snezana; 850 East Greenwich Place, Palo Alto, CA 94303 (US). LABAT, Ivan; 140 Acalanes Drive, Sunnyvale, CA 94086 (US). LESHKOWITZ, Dena; 678 Durshire Way, Sunnyvale, CA 94087 (US). KITA, David; 899 Bounty Drive, Foster City, CA 94404 (US). GARCIA, Veronica; Apartment 412, 396 Ano Nuevo, Sunnyvale, CA 94086 (US). JONES, Lee, William; 396 Ano Nuevo #412, Sunnyvale, CA 94086 (US). STACHE-CRAIN, Birgit; 345 South Mary Avenue, Sunnyvale, CA 94086 (US).</p> <p>(74) Agent: BLACKBURN, Robert, P.; Chiron Corporation, P.O. Box 8097, Emeryville, CA 94662-8097 (US).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.</i>  <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 17 February 2000 (17.02.00)</p>	
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(54) Title: HUMAN GENES AND GENE EXPRESSION PRODUCTS V																		
(57) Abstract																		
<p>This invention relates to novel human polynucleotides and variants thereof, their encoded polypeptides and variants thereof, to genes corresponding to these polynucleotides and to proteins expressed by the genes. The invention also relates to diagnostic and therapeutic agents employing such novel human polynucleotides, their corresponding genes or gene products, e.g., these genes and proteins, including probes, antisense constructs, and antibodies.</p>																		

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# INTERNATIONAL SEARCH REPORT

Intern: al Application No  
PCT/US 99/10602

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 C12N15/12 C07K14/47 C12Q1/68 C07K16/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K C12Q		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YEATMAN ET AL: "Identification of genetic alterations associated with the process of human experimental colon cancer liver metastasis in the nude mouse" CLINICAL & EXPERIMENTAL METASTASIS, vol. 14, no. 3, May 1996 (1996-05), pages 246-252 252, XP002099961 ISSN: 0262-0898 the whole document --- -/--	1-5
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 14 September 1999		Date of mailing of the international search report 22. 12. 99
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer van Klompenburg, W

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	YEATMAN ET AL.: "Identification of a differentially-expressed message associated with colon cancer liver metastasis using an improved method of differential display" NUCLEIC ACIDS RESEARCH, vol. 23, no. 19, 1995, page 4007/4008 8 XP002099962 ISSN: 0305-1048 the whole document ---	1-5
X	CARMECI ET AL: "Identification of a gene (GPR30) with homolgy to the G-protein -coupled receptor superfamily associated with estrogen receptor expression in breast cancer" GENOMICS, vol. 45, no. 3, 1 November 1997 (1997-11-01), pages 607-617 17, XP002099963 ISSN: 0888-7543 the whole document ---	1-5
X	J.H.MORISSEY: "Human tissue factor gene" EMBL DATABANK, ID HSTFPB, 20 February 1989 (1989-02-20), XP002114962 the whole document ---	1-5
A	RADINSKY ET AL: "Level and function of epidermal growth factor receptor predict the metastatic potential of human colon carcinoma cells" CLINICAL CANCER RESEARCH, vol. 1, no. 1, January 1995 (1995-01), pages 19-31 31, XP002099964 ISSN: 1078-0432 the whole document ---	1-5
A	BALDI ET AL: "Differential expression of the retinoblastoma gene family members pRb/p105, p107, and pRb2/p130 in lung cancer" CLINICAL CANCER RESEARCH, vol. 2, no. 2, July 1996 (1996-07), pages 1239-1245 45, XP002099965 ISSN: 1078-0432 the whole document -----	1-5

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 10602

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☒ Claims Nos.: 11  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-5

A library of polynucleotides comprising the sequence information of at least one of the sequences 1-2702.

2. claims: 6-11 all partially

The isolated nucleic acid with SeqIdNo:1, sequences with at least 90% sequence identity therewith and degenerate variants thereof, host comprising said nucleic acid, peptide encoded by said nucleic acid, antibody against said protein, vector comprising said nucleic acid.

3-2708. claims: 6-12, all partially, as far as applicable As invention 2, and when applicable, a method for detecting the differential expression of said nucleic acid, but limited respectively to the SeqIdNo:2-2707.

For the sake of conciseness, the second matter is explicitly defined, but the subject matters of inventions 3-2708 are defined by analogy thereto.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.3

Claims Nos.: 11

The subject matter of claim 11 is not clear. A meaningful search could therefore not be performed for this claim.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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SEQ ID NO:	Sample Name	Overlap	Clone Name
1608	801.F2.sp6:164705	VNO	
1609	801.A3.sp6:164646	VO	M00001355B:A01
1610	801.B3.sp6:164658	VO	M00001358D:D09
1611	801.C3.sp6:164670	VO	M00001359A:B07
1612	801.D3.sp6:164682	VO	M00001362A:C10
1613	801.E3.sp6:164694	VO	M00001362B:A09
1614	801.G3.sp6:164718	VO	M00001365D:D12
1615	801.H3.sp6:164730	VO	M00001365D:H09
1616	801.A4.sp6:164647	VNO	
1617	801.B4.sp6:164659	VO	M00001370A:G09
1618	801.C4.sp6:164671	VO	M00001370B:B04
1619	801.D4.sp6:164683	VO	M00001370B:B12
1620	801.E4.sp6:164695	VNO	
1621	801.G4.sp6:164719	VO	M00001374D:D09
1622	801.D5.sp6:164684	VO	M00001377C:B08
1623	801.F5.sp6:164708	VNO	
1624	801.G5.sp6:164720	VNO	
1625	801.H5.sp6:164732	VNO	
1626	801.A6.sp6:164649	VO	M00001384A:C09
1627	801.B6.sp6:164661	VO	M00001387A:A04
1628	801.D6.sp6:164685	VO	M00001389B:B06
1629	801.E6.sp6:164697	VO	M00001390A:C06
1630	801.F6.sp6:164709	VO	M00001390A:H01
1631	801.D7.sp6:164686	VNO	
1632	801.E7.sp6:164698	VO	M00001399C:E10
1633	1033.A01.sp6:188313	VO	M00001399D:F09
1634	801.G7.sp6:164722	VNO	
1635	801.H7.sp6:164734	VO	M00001401D:D04
1636	801.A8.sp6:164651	VNO	
1637	801.B8.sp6:164663	VO	M00001402D:C07
1638	801.C8.sp6:164675	VO	M00001402D:H03
1639	801.D8.sp6:164687	VO	M00001403B:A01
1640	801.E8.sp6:164699	VO	M00001405D:F05
1641	801.G8.sp6:164723	VO	M00001406C:A11
1642	801.B9.sp6:164664	VO	M00001407B:A08
1643	801.C9.sp6:164676	VO	M00001407D:H11
1644	801.D9.sp6:164688	VNO	
1645	801.E9.sp6:164700	VNO	
1646	801.F9.sp6:164712	VO	M00001411A:D01
1647	801.G9.sp6:164724	VNO	
1648	801.H9.sp6:164736	VO	M00001411C:G02
1649	801.B10.sp6:164665	VO	M00001412A:A11
1650	801.C10.sp6:164677	VNO	

We Claim:

1. A library of polynucleotides, the library comprising the sequence information of at least one of SEQ ID NOS:1-2702.

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2. The library of claim 1, wherein the library is provided on a nucleic acid array.

3. The library of claim 1, wherein the library is provided in a computer-readable format.

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4. The library of claim 1, wherein the library comprises a polynucleotide corresponding to a gene differentially expressed in a cancer cell of high metastatic potential relative to a control cell, wherein the control cell is a normal cell or a cell of low metastatic potential, and wherein the sequence is selected from the group consisting of SEQ ID NOS:1213, 1538, 1466, 1356, 1383, 1158, 441, 1338, 1426, 1547, 1313, 841, 1534, 1503, 829, 1408, 1447, 1389, 356, 1492, 1543, 799, 1437, 1251, 972, 1482, 1299, 109, 1558, 1355, 1548, 250, 919, 358, 1525, 1157, 150, 651, 1298, 57, 625, 1322, 36, 621, 215, 561, 247, 199, 998, 502, 1382, 1181, 1309, 1157, 1260, 1185, 1525, 248, 87, 698, 57, 924, 1249.

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5. The library of claim 1, wherein the library comprises a polynucleotide corresponding to a gene differentially expressed in a cancer cell of low metastatic potential relative to a control cell, wherein the control cell is a normal cell or a cell of high metastatic potential, and wherein the sequence is selected from the group consisting of SEQ ID NOS:248, 726, 14, 699, 763, 20, 79, 715, 991, 1199, 707, 1128, 891, 1146, 731, 1518, 340, 949, 1247, 1185, 924, 822, 728, 341, 1527, 698, 949, 744, 973, 1268, 1114, 1032, 109, 973, 91, 982, 1267, 93, 1556, 1251, 1206, 812, 1254, 1220, 766, 1156, 1007, 981, 762, 876, 1234, 1183, 1044, 785, 1069, 770, 778, 792, 822, 1258, 1224, 984, 841, 339, 1213, 1201, 1192.

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6. An isolated polynucleotide comprising a nucleotide sequence having at least 90% sequence identity to an identifying sequence of SEQ ID NOS:1-2707 or a degenerate variant or fragment thereof.

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7. A recombinant host cell containing the polynucleotide of claim 6.

8. An isolated polypeptide encoded by the polynucleotide of claim 6.

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9. An antibody that specifically binds a polypeptide of claim 8.

10. A vector comprising the polynucleotide of claim 6.

11. A polynucleotide comprising the nucleotide sequence of an insert contained in a clone deposited as ATCC accession number xx, xx, xx, xx, xx, xx, xx, xx, or xx.

5

12. A method of detecting differentially expressed genes correlated with a cancerous state of a mammalian cell, the method comprising the step of:

detecting at least one differentially expressed gene product in a test sample derived from a cell suspected of being cancerous, where the gene product is encoded by a gene corresponding to a sequence of at least one of SEQ ID NOS: 1213, 1538, 1466, 1356, 1383, 1158, 441, 1338, 1426, 1547, 1313, 841, 1534, 1503, 829, 1408, 1447, 1389, 356, 1492, 1543, 799, 1437, 1251, 972, 1482, 1299, 109, 1558, 1355, 1548, 250, 919, 358, 1525, 1157, 150, 651, 1298, 57, 625, 1322, 36, 621, 215, 561, 247, 199, 998, 502, 1382, 1181, 1309, 1157, 1260, 1185, 1525, 248, 87, 698, 57, 924, 1249, 248, 726, 14, 699, 763, 20, 79, 715, 991, 1199, 707, 1128, 891, 1146, 731, 1518, 340, 949, 1247, 1185, 924, 822, 728, 341, 1527, 698, 949, 744, 973, 1268, 1114, 1032, 109, 973, 91, 982, 1267, 93, 1556, 1251, 1206, 812, 1254, 1220, 766, 1156, 1007, 981, 762, 876, 1234, 1183, 1044, 785, 1069, 770, 778, 792, 822, 1258, 1224, 984, 841, 339, 1213, 1201, 1192

wherein detection of the differentially expressed gene product is correlated with a cancerous state of the cell from which the test sample was derived.

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